

# INTERVIEW about Interleukin-12p40 and mycobacterial infections

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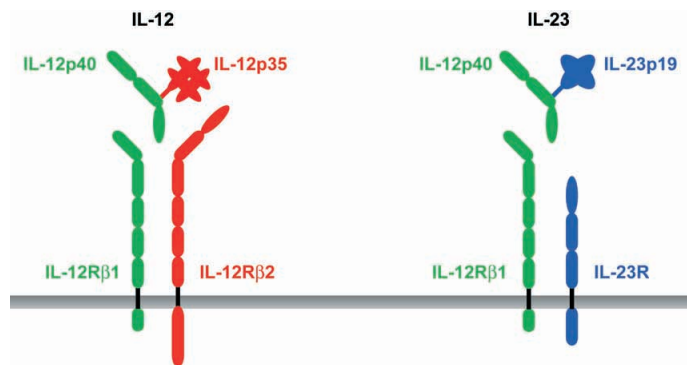
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## What is known until today about IL-12p40?

**Christoph Hölscher:** Interleukin (IL)-12p40 is one component of the heterodimeric cytokines IL-12 and IL-23. IL-12 is composed of the two disulfide-linked subunits IL-12p40 and IL-12p35 (1)(Figure 1).

I transmembrane protein, with sequence homology to the IL-12Rβ2 was identified to build the IL-23R complex which was found to be expressed on T cells, NK cells, macrophages and dendritic cells.



**Figure 1:** IL-12p40-related cytokines. IL-12p40 combines with either p35 or p19 to form the heterodimeric cytokines IL-12 and IL-23, respectively. In this manner, the p40 subunit is shared between IL-12 and IL-23. The receptor complexes for both cytokines also share the IL-12Rβ1 subunit. Whereas the IL-12R comprises the IL-12Rβ1 and the IL-12Rβ2, the IL-23R complex is composed of the IL-12Rβ1 and a IL-23R subunit.

Recently, a p19 protein was identified which also combines with IL-12p40 to form a novel, biologically active cytokine, designated IL-23, with similar but discrete functions from IL-12. At the sequence level, IL-23p19 is most closely related to the IL-12p35 subunit. In this manner, the p40 subunit is shared between IL-12 and IL-23. IL-12 and IL-23 not only share the p40 subunit, both receptor complexes also consist of the IL-12 receptor (R) β1 which binds p40 with high affinity. The IL-12R is primarily expressed on activated T and NK cells and is composed of IL-12Rβ1 and IL-12Rβ2 subunits. In addition to the IL-12Rβ1, another type

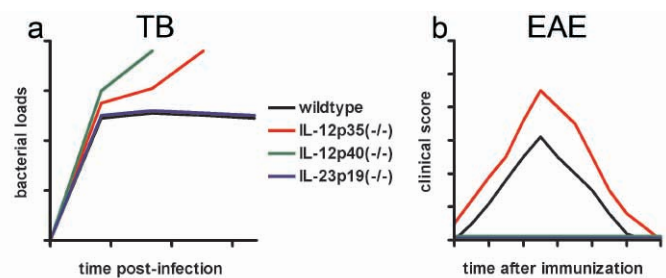
On the functional level, IL-12 drives naive CD4<sup>+</sup> T cells to become Th1 cells that produce interferon-gamma (IFN-γ). An IL-12-driven cell-mediated Th1 immune response is known to be critical in host defence against intracellular infections such as Mycobacteria aiming at efficient activation of macrophages through IFN-γ-dependent mechanisms (1). In contrast to IL-12, IL-23 has been shown to act preferentially on memory immune responses by selectively increasing proliferation of effector/memory T cells, and its role therefore was supposed to be important for the anamnestic immune response.

## Why are genetic defects in IL-12p40-mediated mechanisms responsible for mycobacterial infections?

**Christoph Hölscher:** Because in mice IL-12 induces a cell-mediated Th1 immune response that is critical in host defence against intracellular pathogens, IL-12-deficient IL-12p35<sup>-/-</sup> mice are highly susceptible to mycobacterial infections (2,3). Initially, comparison of data from IL-12p35<sup>-/-</sup> (deficient only in IL-12) and IL-12p40<sup>-/-</sup> (deficient in IL-12 and IL-23) mice provided indirect evidence that IL-23 has an important function in controlling infection with *Mycobacterium tuberculosis* and *Mycobacterium avium* (2,3)(Figure 2a). These studies indicate an antibacterial effector mechanism preserved in IL-12p35<sup>-/-</sup> mice that is absent in IL-12p40<sup>-/-</sup> mice. This IL-23-mediated mechanism is ultimately incapable of fully controlling mycobacterial infection, but significantly delays progression of bacterial proliferation. However, it turned out that IL-12 is able to compensate for IL-23-deficiency as IL-23p19<sup>-/-</sup> mice were completely resistant to mycobacterial infections (4)(Figure 2b). Therefore,

The importance of IL-12p40 in cell-mediated immune responses was also highlighted in humans with genetic deficiencies in IL-12p40 that causes severe defects in cellular immunity and increased susceptibility to intracellular infections (5).

Before IL-23 was known, however, an uncontrolled IL-12-dependent Th1 immune responses (that is protective during mycobacterial infections) was believed to mediate many chronic inflammatory diseases such as autoimmunity. Indeed, targeting the p40 subunit or IL-12Rβ1-mediated signaling has been proven to suppress development and progression of disease in a multitude of experimental models of autoimmunity. Because IL-12 shares the p40 subunit and the IL-12Rβ1 with IL-23, some or all of the effects initially ascribed to inhibition of IL-12 may, in fact, have been due to concurrent blockage of both cytokines, or of IL-23 only, rather than IL-12 (6). Actually, differential analysis of IL-12p35<sup>-/-</sup>, IL-12p40<sup>-/-</sup> and



**Figure 2:** Autoimmunity and infection in IL-12p40<sup>-/-</sup> and IL-23p19<sup>-/-</sup> mice. (a) IL-23p19<sup>-/-</sup> but not IL-12p40<sup>-/-</sup> are resistant to *M. tuberculosis* infection (experimental animals are infected with *M. tuberculosis* per aerosol and the bacterial loads in lungs from infected mice are determined in a mycobacterial colony enumeration assay). (b) IL-12p40<sup>-/-</sup> and IL-23p19<sup>-/-</sup> mice are resistant to EAE (to induces EAE, experimental animals are immunized with a myelin oligodendrocyte glycoprotein peptide and disease progression is monitored).

IL-23 may play a rather secondary role for protection from mycobacterial infections.

IL-23p19<sup>-/-</sup> mice currently question IL-12 as a central mediator of T cell-dependent

autoimmune disorders and put IL-23 in the limelight of inflammation research. In fact, similar to IL-12p40<sup>-/-</sup> mice, IL-23p19<sup>-/-</sup> mice were completely resistant to pathologic autoimmune inflammation in experimental autoimmune encephalitis (EAE)(7)(Figure 2b).

Until the discovery of IL-23, Th1 immune responses involved in autoimmune inflammation and immune protection from infection appeared inextricably interconnected and the

treatment of autoimmunity almost implicitly increased susceptibility to infectious diseases. The finding that IL-12 and IL-23 differentially act during infectious and autoimmune diseases open exciting perspectives for the discovery of drugs that selectively target IL-23 and IL-23-mediated mechanisms in autoimmune inflammation without compromising protective immune responses against pathogens.

### What do you think about IL-12p40 therapy?

**Christoph Hölscher:** Pharmacological interference with IL-12p40 pathways has received widespread attention. Many IL-12p40 inhibitors have been proven effective in limiting or preventing autoimmune diseases. However, neutralization of the p40 subunit in IL-12 and IL-23 not only mitigates autoimmune inflammation, it also affects protection from tuberculosis. As IL-23p19<sup>-/-</sup> mice were shown to display normal immune responses to mycobacterial infections, IL-23, however, may not be as essential for Th1-mediated protection as

previously anticipated. In contrast, IL-23 exclusively induces a distinct IL-17-producing Th cell population that is responsible for autoimmune inflammation (8). Because IL-23 appears to regulate these immune responses differently from IL-12, therapeutic blockade of IL-23 and IL-23-mediated mechanisms rather than interference with IL-12p40-dependent immune responses may provide a superior approach for the treatment of a range of inflammatory autoimmune diseases without compromising host resistance to mycobacterial infections.

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